The claimed invention

Claims 1-19, as amended, are drawn to a composition for the nasal administration of a drug, a device for delivering and a method for using the composition. The drug is in a dry powder form having an average particle size of between 10 and 20 microns, in a dosage formulation suitable for administration to the nasal region. The dry powder form comprises microparticles formed of the drug and one of polymers or diketopiperazines.

One critical aspect of the claims is the ability of the drug particles to be delivered to and remain in the nasal region, which requires the particles to have a size in the range of between 10 and 20 microns. If the particles have a size below 10 microns, the particles will pass the nasal region and go to the pulmonary system; if the particles have a size above 20 microns, the particles would not be delivered to the nasal region.

Hettche

Hettche describes a formulation of azelastine that is suitable for administration to the eye and/or nose (col. 1, lines 37-38). The formulation can be solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols (col. 3, lines 26-28). In the case of powders, the concentration of azelasine base is 0.005 to 2 percent by weight relative to the solid carrier substances (col. 3, lines 37-39). The particle size for an insufflatable powder should not be greater than 20 microns (col. 5, lines 51-53). The carrier substances for solid powder formulation include sugars such as glucose, saccharose, lactose and fructose, starches or their derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinyl pyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives, sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate (col. 5, lines 57-66). The examples describe various solution, aerosol, or ointment formulations

for nasal or eye administration (Examples 1-4).

There is no disclosure of microparticles.

In relevant part, Hettche discloses a dry powder formulation that contains from 0,0005% to 2% azelástine. The azelastine is **mixed with** inert carrier substances or **drawn up onto** inert carrier substances. Hettche does not disclose or teach forming micrparticles of the drug with a polymer or a diketopiperazine by dispersing the drug in the polymer or diketopiperazine. Nor does Hettche disclose or teach encapsulating the drug with a material. As such, Hettche does not anticipate claims 1-19 under 35 U.S.C. 102 (b).

Rejections under 35 U.S.C. 103

Claims 5, 8, and 12 were rejected under 35 U.S.C. §103 as obvious over Hettche in view of U.S. Patent No. 5,352,461 to Feldstein et al. ("Feldstein"). The applicants respectfully traverse this rejection.

One critical aspect of the claims is that the **dry powder** having particle size in the range between 10 to 20 microns so that the drug particles can be delivered to and retain in the nasal region. Feldstein describes a diketopiperazine drug delivery system in the form of microspheres encapsulating bioactive agents for **topical, local or systemic parenteral, or enteral administration** (col. 7, lines 9-11). Therefore, none of Hettche and Feldstein provides the motivation for one of ordinary skill in the art to make and use the claimed subject matter. Moreover, Feldstein teaches particles of between 0.1 to 10 microns (col. 3, lines 21-23), which, to one of ordinary skill in the art, would pass through the nasal region to the pulmonary system (see, Edwards et al., "Recent advances in pulmonary drug delivery using large, porous inhaled particles" in J Appl Physiol 85(2):379-85 (1998) (Review)). Therefore, Feldstein does not provide an enabling disclosure of a dry powder formulation for nasal delivery, which requires the

powder to stay in the nasal region. As such, even if Hettche and/or Feldstein provide one of ordinary skill in the art to make and use dry powder formulations for nasal administration, one still cannot have a reasonable expectation of success of the claimed subject matter, which causes the drug particles to be delivered to and retain in the nasal region.

The Examiner asserted that Felstein is cited for a drug capable of being encapsulated by or dispersed in a diketopiperazine but not for the composition having a particle size in the range from 0.1 nm to 10 nm. The Examiner's position is in direct conflict with MPEP and the rulings of the Federal Circuit. "**A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention**." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. Denied*, 469 U.S. 851 (1984); MPEP § 2141.03 (emphasis added). As discussed above, Felstein teaches drug compositions having a size in the range between 0.1 nm to 10 nm that would not retain at the nasal region, thereby **teaching away** from the claimed composition and the method of making and using thereof as defined in claims 5, 8, and 12. As such, Hettche in combination with Felstein does not make obvious claims 5, 8, and 12 under 35 U.S.C. 103 (see *Hodosh v. Block Drug Co. Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182 n.5 (Fed. Cir. 1986; see also MPEP § 2141). For the same reason, nor does Hettche in combination of Felstein makes obvious claims 1-4, 6, 7, 9-11 and 13-19 under 35 U.S.C. 103.

Allowance of claims 1-19 is therefore earnestly solicited. A copy of the claims as pending is attached as appendix for the Examiner's convenience.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)

I hereby certify that this Amendment and Response to Office Action, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

Date: September 10, 2002

Patrea L. Pabst

APPENDIX I: Marked-up Copy of Claims as Pending

1. (amended) A composition for the nasal administration of a drug [to a patient comprising

a drug]in a dry powder form having an average particle size of between 10 and 20 microns, in a dosage formulation suitable for administration to the nasal region,

the dry powder form comprising microparticles formed of the drug and a polymer or diketopiperazine.

2. The composition of claim 1 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

3. The composition of claim 2 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

4. The composition of claim 1 wherein the drug is formulated in a polymeric carrier.

5. The composition of claim 1 wherein the drug is formulated in a diketopiperazine formulation.

6. The composition of claim 1 wherein the dry powder formulation consists essentially of drug.

7. (amended) A drug delivery device for nasal administration comprising

a drug in a dry powder form having an average particle size of between 10 and 20 microns, in a dosage formulation for administration to the nasal region, and

a device for delivering a measured dose of the drug to the nasal mucosa,

wherein the dry powder form comprises microparticles formed of the drug and a polymer or diketopiperazine.

8. The device of claim 7 wherein the device is a nasal insufflator.

9. The device of claim 7 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

10. The device of claim 7 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

11. The device of claim 7 wherein the drug is formulated in a polymeric carrier.

12. The device of claim 7 wherein the drug is formulated in a diketopiperazine formulation.

13. The device of claim 7 wherein the dry powder formulation consists essentially of drug.

14. (amended) A method of administering a drug to the nasal region of a patient in need thereof, comprising nasally administering a dry powder form of a drug having an average particle size of between 10 and 20 microns, in a dosage formulation suitable for nasal administration,

wherein the dry powder form comprises microparticles formed of the drug and a polymer or diketopiperazine.

15. The method of claim 14 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

16. The method of claim 14 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

17. The method of claim 14 wherein the drug is formulated in a polymeric carrier.

18. The method of claim 14 wherein the drug is formulated in a diketopiperazine formulation.

19. The method of claim 14 wherein the dry powder formulation consists essentially of drug.